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## Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children (Review)

Hahn S, Kim Y, Garner P

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Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children.

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[Intervention Review]

# Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

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## ABSTRACT

### Background

Oral rehydration solution (ORS) has reduced childhood deaths from diarrhoea in many countries. Recent studies suggest that the currently recommended formulation of ORS recommended by the World Health Organization (WHO) may not be optimal, and solutions that contain lower concentrations of sodium and glucose may be more effective.

### Objectives

To compare reduced osmolarity ORS with WHO standard ORS in children with acute diarrhoea.

### Search methods

CENTRAL (*The Cochrane Library*, Issue 3, 2004), MEDLINE (1966 to July 2004), EMBASE (1988 to July 2004), and Current Contents (July 2004) were searched. Additional trials were identified by hand searching. Content experts were contacted.

### Selection criteria

Randomized controlled trials comparing reduced osmolarity ORS with the WHO standard ORS formulation. The primary outcome was unscheduled intravenous fluid infusion. Secondary outcomes were measures of clinical illness.

### Data collection and analysis

Two reviewers extracted data. We tested for heterogeneity using the Chi-square statistic, conducted sensitivity analysis by allocation concealment, and the regression approach to assess funnel plot asymmetry from selective trial publication.

### Main results

The primary outcome, unscheduled intravenous fluid infusion, was reported in 11 trials. In a meta-analysis of 8 trials, reduced osmolarity ORS was associated with fewer unscheduled intravenous fluid infusions compared with WHO standard ORS (Mantel Haenzel odds ratio 0.59, 95% confidence interval 0.45 to 0.79) with no evidence for heterogeneity between trials. No unscheduled intravenous fluid infusion therapy was required in any participant in three trials.

Eleven trials reported stool output, and data suggested less stool output in the reduced osmolarity ORS group. Vomiting was less frequent in the reduced osmolarity group in the six trials reporting this. Six trials sought hyponatraemia, with events in three studies, but no obvious difference between the two arms.

## Authors' conclusions

In children admitted to hospital with diarrhoea, reduced osmolarity ORS when compared to WHO standard ORS is associated with fewer unscheduled intravenous fluid infusions, lower stool volume post randomization, and less vomiting. No additional risk of developing hyponatraemia when compared with WHO standard ORS was detected.

## PLAIN LANGUAGE SUMMARY

### Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Children with diarrhoea lose body water and sometimes become dehydrated. A solution of sugar and salt dissolved in water is widely used to treat dehydration caused by diarrhoea. This reviews shows that a solution of lower osmolarity than the current international standard means fewer children subsequently require an intravenous drip.

## BACKGROUND

Diarrhoea remains a leading cause of childhood death in middle and low income countries. The main complication is dehydration, which was treated with intravenous fluid infusion until the early 1960s. Oral rehydration solution (ORS) is now the mainstay of therapy and is particularly useful when intravenous fluids are in short supply, health services are basic, and there is a shortage of skilled personnel (Almroth 1995). The combination of salt and sugar enhances fluid absorption because sodium and glucose transport in the small intestine are coupled, and glucose promotes absorption of both sodium ions and water (Fordtran 1968). Diarrhoea is caused by derangement of fluid absorption and secretion from the gut, and coupling sodium and glucose allows absorption, even during active fluid secretion due to infection. Thus rehydration can take place even with large fluid losses, as seen in enterotoxic diarrhoea, such as that caused by cholera or infection with *Escherichia coli* (Guarino 2001).

ORS has proved both safe and effective worldwide in hospital settings, and is now widely used in the home to prevent dehydration (Mahalanabis 1973, Grant 1983). For more than two decades, the World Health Organization (WHO) has recommended the standard formulation of glucose-based ORS with 90 mmol/L of sodium and 111 mmol/L of glucose and a total osmolarity of 311 mmol/L. It remains unclear however, whether this is the optimum level of sodium. Laboratory work suggests that lower concentrations of sodium and glucose enhance solute induced water absorption (Farthing 1988, Hunt 1992). Papers report patients experiencing blood sodium levels above the normal of 150 mmol/L with standard solution (Finberg 1973).

The objective of this review is to critically appraise and evaluate all relevant randomized controlled trials addressing comparative

effects of reduced osmolarity ORS with WHO standard ORS. One potential adverse effect of reduced osmolarity ORS is a deficiency of sodium in the blood (hyponatraemia), which can give rise to convulsions. We are also exploring the risk of this adverse outcome through trial and observational data.

We confined the review to children, as they are most vulnerable to dehydration and electrolyte imbalance from diarrhoea, and are the targets for large primary care child investments that include ORS sachet distribution. Severity, duration, and volume of diarrhoea are often primary outcomes in clinical ORS studies, but we sought a pragmatic outcome relevant to health providers. ORS aims to rehydrate children and avoid the need for intravenous fluid infusion. We therefore identified unscheduled intravenous fluid infusion as a primary outcome as this represents failed oral therapy.

## OBJECTIVES

To compare reduced osmolarity oral rehydration solution with the World Health Organization recommended strength for treating diarrhoea in children.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials, defined as a trial in which the subjects followed were assigned prospectively to one of two or more interventions by random allocation. This excludes quasi-randomized designs.

### Types of participants

Children with acute diarrhoea (history of less than 5 days).

### Types of interventions

Experimental: Reduced osmolarity oral rehydration solution (total osmolarity 250 mmol/L or less with reduced sodium).

Control: World Health Organization standard oral rehydration solution (90 mmol/L sodium, 111mmol/L glucose, total osmolarity 311 mmol/L).

### Types of outcome measures

#### Primary outcomes

Need for unscheduled intravenous fluid infusion during the course of treatment.

#### Secondary outcomes

- Stool output.
- Children vomiting during rehydration.
- Asymptomatic hyponatraemia (defined as serum sodium less than 130mmol/L) during follow up.

### Search methods for identification of studies

We used the following search terms to search all trial registers and electronic databases: child; diarrhoea; fluid therapy; oral rehydration; osmolar; and rehydration solutions.

We searched the following trial register: Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 3, 2004).

We searched the following electronic databases: MEDLINE (1966 to July 2004); EMBASE (1988 to July 2004); and Current Contents (July 2004).

We also checked the citations of existing reviews and trial reports. For unpublished data and ongoing trials, we contacted current researchers and key agencies, including the World Health Organization, the Centers for Disease Control and Prevention, Atlanta (USA), and the International Centre for Diarrhoeal Disease Research, Bangladesh.

### Data collection and analysis

#### Selection of studies

SH and SK independently applied the inclusion criteria to all identified trials, and differences were resolved by discussion with the PG.

#### Data extraction and management

SH and SK extracted data on relevant outcome measures using a standardized data abstraction form.

#### Assessment of risk of bias in included studies

Each included trial was assessed in terms of adequacy of concealment of allocation, generation of allocation sequence, blinding, and follow up of patients, using the guidelines of the Cochrane Infectious Diseases Group. Studies excluded were detailed in the '[Characteristics of excluded studies](#)'.

#### Data synthesis

We used the Mantel-Haenszel odds ratio (OR) for binary outcomes. The odds ratios were not estimated when neither intervention group found any event, which are indicated in the MetaView figures. We used the Standardized Mean Difference (SMD) for continuous outcomes. We combined studies using a fixed effect method. For all estimates, we calculated 95% confidence intervals. We tested statistical heterogeneity using Chi-square statistic with a P-value less than 0.1 indicating statistical significance. We had prespecified potential sources of heterogeneity for analysis. We examined publication bias using a funnel plot, and a regression approach ([Egger 1997](#)) to assess funnel plot asymmetry. We conducted a sensitivity analysis in relation to adequate allocation concealment.

After presentation of the results, an expert consultation group from the World Health Organization recommended a stratified analysis by mmol sodium (less than 75 mmol and 75 to 85 mmol), and this analysis is now included ([WHO 2001](#)).

## RESULTS

### Description of studies

We identified 41 studies for inclusion, and 16 studies met the inclusion criteria. The progress through the stages of meta-analysis, using the process suggested in the QUOROM statement ([QUOROM Group 1999](#)), is shown below.

41 studies comparing oral rehydration solution (ORS) formulation for treating diarrhoea.

- 6 excluded as not randomized controlled trials (RCTs);

35 remaining RCTs of ORS comparing formulation for treating diarrhoea patients.

- 9 excluded as intervention was something other than reduced osmolarity ORS;

26 remaining RCTs reporting reduced osmolarity ORS in one treatment arm.

- 6 excluded if control group did not use World Health Organization (WHO) standard ORS;

20 remaining RCTs reporting comparison of reduced osmolarity ORS with WHO standard ORS.

- 2 excluded as not in children;

18 remaining RCTs reporting comparison of reduced osmolarity ORS with WHO standard ORS for treating children with diarrhoea.

- 2 excluded as no relevant outcomes reported;

16 remaining RCTs reporting comparison of reduced osmolarity ORS with WHO standard ORS in children with diarrhoea in relation to need of unscheduled intravenous fluid infusion therapy and some measures of clinical illness.

- 2 excluded (Mexico 1988, Mexico 1990b) as they appear to be duplicates of a third trial (Mexico 1990a). We have contacted the authors, but while awaiting clarification, we have included only the paper with the largest number of patients (Mexico 1990a).

13 remaining RCTs. As one paper reported on two trials, one in the USA and one in Panama, we present these as separate studies (Panama 1982, USA 1982).

This leaves a total of 14 included studies. These were from Egypt (2), Bangladesh (3), Mexico (1), Colombia (1), India (3), Panama (1), and the USA (1). Two other studies were multicentre trials; one was conducted in Brazil, India, Mexico, and Peru, and the other in Bangladesh, Brazil, India, Peru, and Vietnam.

Participants were children with acute non-cholera diarrhoea in all trials except three, which included cholera patients (Bangladesh 1995b, CHOICE 2001, India 2000b). In all but one which included children up to 5 years old (India 2000a), the participants' ages ranged between 1 and 36 months. All children had some degree of clinical dehydration. One trial treated all children on day 1 with intravenous fluid infusion, and those still producing 80 ml/kg/24h were then randomized (Bangladesh 1995a). In five trials (CHOICE 2001, India 2000b, Panama 1982, WHO 1995, USA 1982) severely dehydrated children were included. Five trials included malnourished children (Bangladesh 1995b, Colombia 2000, Bangladesh 1995b, India 2000a, India 2000b, Mexico 1990a). The number of breastfed children was reported in eight trials (Bangladesh 1995a, Bangladesh 1995b, Bangladesh

1996a, CHOICE 2001, Colombia 2000, Egypt 1996b, India 2000b, WHO 1995). Fully weaned children were included in one trial (Egypt 1994).

We deviated slightly from the osmolarity definitions in our peer refereed protocol published in The Cochrane Library. For reduced osmolarity, we had defined this to be lower than 250 mmol/L, but some studies defined this as higher, and we therefore extended our limit to a total osmolarity of 270 mmol/L. For the WHO standard ORS, defined as a total osmolarity of 311 mmol/L, we also included two studies that used a slightly different WHO standard ORS with a total osmolarity of 331 mmol/L but with the same sodium and glucose combination (Panama 1982, USA 1982). All but two trials used a glucose based reduced osmolarity ORS; one used sucrose (Bangladesh 1996a), and one used L-alanine with glucose (Bangladesh 1995a).

## Risk of bias in included studies

### Allocation

All of the studies were randomized controlled trials. Nine reported methods that assured adequate allocation concealment (WHO 1995, CHOICE 2001, Colombia 2000, Egypt 1996b, Bangladesh 1995a, Bangladesh 1995b, Bangladesh 1996a, India 2000a, India 2000b).

### Blinding

Six studies (CHOICE 2001, Egypt 1996b, Bangladesh 1995b, Bangladesh 1996a, India 2000a, India 2000b) were double blinded. One of the Mexico studies was described as single blinded (Mexico 1990b), but this study is currently excluded from the analysis as it is thought to be a subset of patients reported in another paper which is included, where no details of blinding are given (Mexico 1990a). Eight studies did not mention blinding.

### Inclusion of all randomized participants

Included trials had losses to follow up of less than 10% of randomized participants in all cases.

## Effects of interventions

Meta-analyses of the four outcomes are illustrated in the MetaView summary analysis.

Information for the primary outcome of the need for unscheduled intravenous fluid infusion was found in 11 trials (n = 1996). In the meta-analysis of 8 trials, a statistically significant reduction for unscheduled intravenous infusion for participants receiving reduced osmolarity oral rehydration solution (ORS) when compared with

World Health Organization (WHO) standard ORS was demonstrated (odds ratio 0.59, 95% confidence interval 0.45 to 0.79). 3 of the 11 trials reported that none of their patients needed intravenous fluid infusion in either group, and the odds ratios were not calculated for these trials.

11 trials reported stool output during rehydration. These trials measured stool output in various ways using different units. We therefore used the standardized mean difference to analyse these data. Since the stool output in diarrhoeal disease showed a positive skewed distribution with clinical improvement, we used a log-normal approximation. The pooled standardized mean difference in the log scale is -0.23 (95% confidence interval -0.33 to -0.14), which suggests that the reduced osmolarity ORS resulted in significantly less stool output when compared with the WHO standard ORS. Data from one trial (India 2000a) were not combined with the others in the meta-analysis because this trial measured stool output for a much longer period beyond rehydration phase. The individual results of all 12 trials are summarized in Appendix 1. For children vomiting during rehydration, six trials reported these data. The tendency was for fewer patients to vomit in the reduced osmolarity ORS group (Odds ratio 0.71, 95% confidence interval 0.55 to 0.92).

For presence of hyponatraemia, six trials reported this outcome. Three of these six trials did not observe hyponatraemia in any participants, irrespective of their allocated group. The meta-analysis of three trials, during which participants developed hyponatraemia, showed no significant difference between the groups (odds ratio 1.45, 95% confidence interval 0.93 to 2.26).

We tested for statistical heterogeneity of treatment effect across trials using the Chi-square statistic for all meta-analyses, and the statistic is presented in each meta-analysis diagram. Results suggest no evidence of statistical heterogeneity (P-value > 0.1) for any outcome considered.

A funnel plot was prepared with the primary outcome. The regression method used to assess funnel plot asymmetry yielded an intercept of -0.104 with a P-value of 0.12, indicating no significant evidence of publication bias.

Sensitivity analysis carried out included studies where allocation concealment was clearly described as adequate and suggested little difference from the original meta-analysis. For example, the pooled odds ratios of the seven trials for the primary outcome with adequate allocation concealment was 0.61 (95% confidence interval 0.46 to 0.82).

A stratified analysis by sodium content of the ORS is presented. Hyponatraemia was not detected in the three studies examining the very low sodium ORS.

## DISCUSSION

We intended to examine treatment effects in cholera subgroup compared with non-cholera diarrhoea. A Cochrane Review of rice-

based rehydration compared with glucose oral rehydration solution (ORS) showed that rice water was associated with lower stool volumes in cholera patients but not in diarrhoea from other causes (Fontaine 2000). The available data were insufficient however. Three studies (CHOICE 2001, Bangladesh 1995b, India 2000b) involved cholera patients, but a subgroup analysis for cholera patients was not available for meta-analysis. There were two studies (Farugue 1996, Alam 1999) in patients with cholera excluded from this review because they were in adults. Any recommendation for rehydration treatment for adults with cholera will need to take these and any other trials found through careful systematic searching into account.

This review examines trials of children admitted to hospital who were dehydrated because of diarrhoea. The trials do not provide any direct evidence for or against the use of ORS at home to prevent dehydration developing; nor do they provide any direct evidence that reduced osmolarity ORS is more effective in preventing dehydration in home-based care in this group.

We stand by our selection of unscheduled intravenous fluid infusion rather than volume of diarrhoea as the primary outcome, as specified in the original protocol. Some specialists consider that volume of diarrhoea is more appropriate, probably because it reflects the animal and human perfusion experiments that provide part of the rationale for a reduced osmolarity ORS. Unscheduled intravenous fluid infusion is pragmatic; it provides a measure of failed oral rehydration and has implications for the healthcare resources. For these reasons, we preserved this as the primary outcome.

When we reviewed the studies for inclusion, most trials reported unscheduled intravenous fluid infusion in the details of trial implementation, where exclusions and dropouts were described. As this was identified as our primary outcome at the protocol stage, we sought out these data and presented them as the primary analysis, and it is our opinion this shows a clear effect. This highlights the value for careful attention to the protocol for a systematic review before examining the trials, and provides an illustration of how non-specialist viewpoints can actually help in obtaining practical and useful answers from meta-analysis.

We found that reduced osmolarity ORS has beneficial effects over the WHO standard ORS in reducing needs for unscheduled intravenous fluid infusion, stool output during rehydration, and the number of patients with vomiting during oral rehydration treatment. Reduced osmolarity ORS has no further risk of developing hyponatraemia as compared to the WHO standard ORS. We are currently exploring the feasibility of obtaining data on convulsions (as evidence of symptomatic hyponatraemia) for the authors of the largest trial (CHOICE 2001).

The research evidence presented here relates to the ORS used for treating children with dehydration. ORS is used much more widely for preventing dehydration developing in children with di-



arrhoea. While this seems appropriate, the applicability to prevention is a judgement, and highlights the need for a systematic review to examine the policies of ORS provision and ORS formula in preventing dehydration in children with diarrhoea.

Findings from this review indicate reduced osmolarity ORS is more effective than WHO standard ORS in the first line treatment of dehydration in children with diarrhoea. It is not easy to be sure however, that this finding applies to a subgroup of patients with severe diarrhoea caused by cholera, where electrolyte loss is profound. This could increase the risk of hyponatraemia, result in adverse clinical events, and attenuate the advantages of reduced osmolarity ORS.

There is the possibility that policymakers and clinicians will judge that cholera reverses the balance of benefits and harms (that is, hyponatraemia will be more common, and outweigh the advantages of reduced osmolarity solution). If this is the case, then one option is to provide WHO standard ORS for people with suspected cholera, or in areas where cholera is prevalent. This is likely to be a logistical problem in areas where diarrhoea is common and coexists with cholera. The single formula sachet aids implementation of this lifesaving intervention. Providing different formulations complicates distribution. It means health workers have a more complicated task in providing the appropriate ORS. These factors may actually impair the effective delivery of any ORS to children.

Policymakers need to be careful if they decide against change a shift to reduced osmolarity solution in areas where cholera is common because of a putative risk around hyponatraemia. If they do this, then they are obliged to prove or disprove their belief in the superiority of WHO standard ORS through a randomized controlled trial in children with clinical cholera. The WHO has convened an expert working group to consider this review and related evidence. The group recommended that ORS for treating diarrhoea in children with non-cholera diarrhoea will be enhanced by shifting to a reduced osmolarity ORS, and propose a global shift to ORS with

an osmolarity of 75 mEq/L of sodium (WHO 2001).

## AUTHORS' CONCLUSIONS

### Implications for practice

Oral rehydration solution (ORS) has saved many children's lives in low and middle income countries, and the sachets are widely used in primary care, based on standards set by the World Health Organization (WHO). This review summarized data from existing studies, and provide some evidence that dehydrated children given a solution with a lower osmolarity were less likely to need an intravenous infusion than those given WHO standard ORS. These results have important implications for policy, and WHO and UNICEF, based on this review, related data, and expert discussions, are recommending reduced osmolarity ORS be accepted as standard (WHO 2001).

### Implications for research

We found insufficient data on cholera in children to make recommendations for this condition. Since cholera is a secretory diarrhoea and electrolyte loss is profound, if reduced osmolarity ORS is to be used in cholera, more trials to investigate this should be undertaken.

There is a need for a good systematic review examining the influence of policies of ORS provision in preventing dehydration and hospital admissions in children with diarrhoea.

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**Finland 1997 {published data only}**

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**Finland 1998 {published data only}**

Rautanen T, Isolauri E, Salo E, Vesikari T. Management of acute diarrhoea with low osmolarity oral rehydration solutions and *Lactobacillus* strain GG. *Archives of Disease in Childhood* 1998; **79**:157–60.

**France 1990 {published data only}**

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Valentiner-Branth P, Steinsland H, Gjessing HK, Santos G, Bhan MK, Dias F, et al. Community-based randomized controlled trial of reduced osmolarity oral rehydration solution in acute childhood diarrhea. *Pediatric Infectious Diseases Journal* 1999; **18**:789–95.

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**USA 1972 {published data only}**

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Bangladesh 1995a

|               |  |
|---------------|--|
| Methods       | RCT  |
| Participants  | 55 children 2 to 15 months old<br>Randomized after 1 day of rehydration<br>Dehydration status not known                  |
| Interventions | 1. Low L-alanine and glucose ORS (255 mosmol/L)<br>2. IV<br>3. WHO standard ORS  |
| Outcomes      | Stool output (24 h, 96 h)<br>Unscheduled IV<br>Fluid intake<br>Food intake<br>Vomiting<br>Body weight<br>Stool frequency |
| Notes         | -  |

#### Bangladesh 1995b

|               |   |
|---------------|---|
| Methods       | RCT (double blind)  |
| Participants  | 50 children 5 to 24 months old with diarrhoea and mild to moderate dehydration<br>Some with cholera |
| Interventions | 1. Low osmolarity glucose ORS (249 mosmol/L)<br>2. WHO standard ORS                                 |
| Outcomes      | Stool output (24 h, 48 h)<br>Stool frequency<br>Fluid intake<br>Patients vomiting                   |
| Notes         | -   |

### Bangladesh 1996a

|               |   |
|---------------|---|
| Methods       | RCT (double blind)  |
| Participants  | 46 children 6 to 30 months with diarrhoea and mild to moderate dehydration (WHO)                        |
| Interventions | 1. Low osmolarity sucrose ORS (198 mosmol/L after full hydrolysis -> 257 mosm/L)<br>2. WHO standard ORS |
| Outcomes      | Stool output (24h, 48 h)<br>ORS intake<br>Unscheduled IV<br>Urine output<br>Stool frequency             |
| Notes         | -   |

### CHOICE 2001

|               |  |
|---------------|--|
| Methods       | RCT (double blind)   |
| Participants  | 671 children<br>1 to 24 months old with diarrhoea and some more severe dehydration   |
| Interventions | (1) Low osmolarity glucose ORS<br>(245 mosmol/L)<br>(2) WHO standard ORS   |
| Outcomes      | Stool output (24 h and total)<br>ORS intake (24 h, total)<br>Vomiting in first 24 h<br>Unscheduled IV in the first 24 h<br>Frequency of hyponatraemia at 24 h<br>Duration of diarrhoea |
| Notes         | -  |

### Colombia 2000

|               |   |
|---------------|---|
| Methods       | RCT   |
| Participants  | 140 boys 1 to 36 months old with diarrhoea and mild or moderate dehydration   |
| Interventions | 1. Low osmolarity glucose ORS (245 mosmol/L)<br>2. WHO standard ORS   |
| Outcomes      | Stool output rate at 24 h<br>Fluid and food intake<br>Weight gain<br>Sodium and potassium levels<br>Urine and vomit outputs |

**Colombia 2000** (Continued)

|       |                            |
|-------|----------------------------|
|       | Vomiting<br>Unscheduled IV |
| Notes | -                          |

**Egypt 1994**

|               |   |
|---------------|---|
| Methods       | RCT, no details given   |
| Participants  | 61 children 3 to 24 months old with diarrhoea and moderate dehydration (WHO definition)               |
| Interventions | 1. Low osmolarity glucose ORS (210 mosmol/L)<br>2. WHO standard ORS<br>3. IV infusion                 |
| Outcomes      | Stool volume at 24 h<br>Fluid intake<br>Weight gain at 6 h<br>Hyponatraemia;<br>Duration of diarrhoea |
| Notes         | -   |

**Egypt 1996b**

|               |  |
|---------------|--|
| Methods       | RCT (double blind)   |
| Participants  | 190 boys 1 to 24 months with diarrhoea and dehydration (WHO criteria)  |
| Interventions | 1. Low osmolarity glucose ORS (245 mosmol/L)<br>2. WHO standard ORS  |
| Outcomes      | Stool output (24 h and total)<br>Fluid intake<br>Sodium<br>Potassium<br>Weight gain<br>Children who vomited<br>Mean weight gain<br>Duration of diarrhoea<br>Treatment failures |
| Notes         | -  |

**India 1984a**

|               |   |
|---------------|---|
| Methods       | RCT   |
| Participants  | 65 infants 0 to 3 months old with acute non-cholera diarrhoea and dehydration   |
| Interventions | 1. Low osmolarity glucose ORS (270 mosmol/L)<br>2. WHO standard ORS (330 mmol/L)<br>3. IV Ringer's lactate therapy  |
| Outcomes      | Stool output (8 h, 24 h)<br>Weight gain<br>Fluid intake<br>Unscheduled IV<br>Haematologic and electrolyte measures<br>Urine output<br>Duration of diarrhoea after hospitalization |
| Notes         | -   |

**India 2000a**

|               |   |
|---------------|---|
| Methods       | RCT<br>(double blind)   |
| Participants  | 70 children 3 to 24 months with acute non-cholera diarrhoea and some dehydration  |
| Interventions | 1. Low osmolarity glucose ORS (224 mosmol/L)<br>2. WHO standard ORS   |
| Outcomes      | Number (%) of patients cured within 10 days<br>Duration of diarrhoea<br>Stool output (g/kg/d)<br>Intake of ORS (ml/kg/d)<br>Fluid intake (ORS + water + liquid food)<br>% of weight gain<br>Mean serum electrolytes |
| Notes         | -   |

**India 2000b**

|               |   |
|---------------|---|
| Methods       | RCT (double blind)  |
| Participants  | 170 children<br>3 months to 5 years old with acute cholera and non-cholera diarrhoea and some to severe dehydration |
| Interventions | 1. Low osmolarity glucose ORS (245 mosmol/L)<br>2. WHO standard ORS   |



**India 2000b** (Continued)

|          |   |
|----------|---|
| Outcomes | Rehydration frequency (stool/4h)<br>Rehydration ORS consumed (L)<br>Rehydration duration (h)<br>Maintenance frequency (stools/4h)<br>Maintenance ORS consumed (L)<br>Maintenance duration (h)<br>Overall frequency (stool/4h)<br>Overall ORS consumed (L)<br>Overall duration (h)<br>Weight gain (%)<br>Caloric intake (kcal/kg/d)<br>Serum sodium (mEq/L)<br>Urine output (boys) (ml/k/h)<br>Intravenous fluid (ml/kg) |
| Notes    | -   |

**Mexico 1990a**

|               |  |
|---------------|--|
| Methods       | RCT  |
| Participants  | 186 children 1 to 36 months old with diarrhoea and dehydration         |
| Interventions | 1. Low osmolarity glucose ORS-90 (240 mosmol/L)<br>2. WHO standard ORS |
| Outcomes      | Need of IV<br>Sodium<br>Potassium concentration                        |
| Notes         | -  |

**Panama 1982**

|               |   |
|---------------|---|
| Methods       | RCT   |
| Participants  | 94 well nourished children 3 months to 2 years old with diarrhoea and dehydration   |
| Interventions | 1. Low osmolarity glucose ORS (251 mosmol/L)<br>2. WHO standard ORS (331 mosmol/L)<br>3. IV   |
| Outcomes      | Stool output (8 h and total illness)<br>Unscheduled IV<br>Fluid and electrolyte intake<br>Weight gain<br>Duration of diarrhoea after discharge<br>Hyponatraemia |

**Panama 1982** (Continued)

|       |                                   |
|-------|-----------------------------------|
|       | Serum sodium<br>Stool electrolyte |
| Notes | -                                 |

**USA 1982**

|               |   |
|---------------|---|
| Methods       | RCT   |
| Participants  | 52 well nourished children 3 months to 2 years old with diarrhoea and dehydration   |
| Interventions | 1. Low osmolarity glucose ORS (251 mosmol/L)<br>2. WHO standard ORS (331 mosmol/L)<br>3. IV   |
| Outcomes      | Stool output (8 h and total illness)<br>Unscheduled IV<br>Fluid and electrolyte intake<br>Weight gain<br>Duration of diarrhoea after discharge<br>Hyponatraemia<br>Serum sodium |
| Notes         | -   |

**WHO 1995**

|               |  |
|---------------|--|
| Methods       | Multicentred RCT (double blind)  |
| Participants  | 447 children aged 1 to 24 months admitted to hospital with diarrhoea and mild to moderate dehydration (WHO classification)   |
| Interventions | 1. Low osmolarity glucose ORS (224 mosmol/L)<br>2. WHO standard ORS  |
| Outcomes      | Stool output at 24 h<br>Fluid intake<br>Mean daily consumption of formula milk and semi-solid food.<br>Weight gain<br>Serum sodium on admission and at 24 h<br>Need for unscheduled IV |
| Notes         | Brazil, Peru, Mexico, India  |

Unscheduled IV: unscheduled intravenous fluid infusion; ORS: oral rehydration solution; RCT: randomized controlled trial; WHO: World Health Organization.

## Characteristics of excluded studies *[ordered by study ID]*

| Study                            | Reason for exclusion   |
|----------------------------------|--|
| <a href="#">Australia 1990</a>   | They compared ORS-26 (total 340 mosmol/L, sodium 26 mmol/L, glucose 2.7%) and ORS-60 (total 240 mosmol/L, sodium 60 mmol/L, glucose 1.8%). The ORS-26 was not WHO standard ORS   |
| <a href="#">Australia 1993</a>   | They compared Glucolyte (total 343 mosmol/L, sodium 26 mmol/L, glucose 145 mmol/L) and Gastrolyte (total 240 mosmol/L, sodium 60 mmol/L, glucose 90 mmol/L). The Glucolyte was not WHO standard ORS. This was not an RCT but an open-label study                       |
| <a href="#">Bangladesh 1978</a>  | They compared two isotonic sucrose (111 mmol/L) based and glucose (111 mmol/L) based ORS solutions. They did not use reduced osmolarity ORS  |
| <a href="#">Bangladesh 1991</a>  | Maltodextrin containing ORS and WHO standard ORS were compared. They did not clearly report the composition of fluid or exact osmolarities but only mentioned 50 g of maltodextrin was added in the place of glucose which suggests no reduced osmolarity ORS was used |
| <a href="#">Bangladesh 1996b</a> | In this RCT, they compared WHO standard ORS (311 mosmol/L) and low osmolar ORS (249 mosmol/L). This was excluded because the study was performed in adult patients   |
| <a href="#">Bangladesh 1999</a>  | This is a RCT comparing WHO standard ORS and low osmolarity ORS. This was excluded because this study was performed in adult patients  |
| <a href="#">Costa Rica 1987</a>  | They compared solution A (WHO standard ORS, 311 mosmol/L) and solution B (Pedialyte total 309 osmol/L). They did not use reduced osmolarity ORS  |
| <a href="#">Ecuador 1995</a>     | This community study was not a RCT but a crossover design in 4 communities. They compared glucose based ORS (310 to 330 mosmol/L) and rice based ORS (220 to 240 mosmol/L). None of their outcomes were relevant for this review.                                      |
| <a href="#">Egypt 1996a</a>      | The intervention group was maltodextrin ORS, and therefore does not meet the inclusion criteria  |
| <a href="#">Finland 1985</a>     | ORS-60 (total 304 mosmol/L, sodium 60 mmol/L, glucose 144 mmol/L) and WHO standard ORS (total 331 mosmol/L) were used. ORS-60 was not a reduced osmolarity ORS   |
| <a href="#">Finland 1986</a>     | They compared two glycine supplemented ORS (total osmolarity 360 mmol/L and 280 mmol/L) and an ORS with sodium 60 mmol/L (total osmolarity 304 mmol/L). They did not use reduced osmolarity ORS or WHO standard ORS  |
| <a href="#">Finland 1993</a>     | Two ORS-60 solutions (sodium 60 mmol/L, each) were compared. One is isotonic (304 mosmol/L and has higher glucose concentration (144 mmol/L), the other hypo-osmolar solution (224 mosmol/L) has 84 mmol/L of glucose. They did not use WHO standard ORS               |
| <a href="#">Finland 1997</a>     | They compared one standard ORS (sodium 60 mmol/L, total 304 mosmol/L) and the low osmolarity ORS (sodium 60 mmol/L, total 224 mosmol/L). They did not use WHO standard ORS   |
| <a href="#">Finland 1998</a>     | Two hypotonic ORS with osmolarities of 224 osmol/L (sodium 60 mmol/L, glucose 84 mmol/L) and 204 mosmol/L (sodium 60 mmol/L, glucose 64 mmol/L) were compared. They did not use WHO standard ORS   |

(Continued)

|                    |  |
|--------------------|--|
|                    | and this was not a RCT but an alternate allocation trial   |
| France 1990        | They compared solution A (total 326 osmol/L, sodium 49 mmol/L, glucose 110 mmol/L) and solution D (total 240 osmol/L, sodium 60 mmol/L, glucose 90 mmol/L). They did not use WHO standard ORS  |
| Guinea-Bissau 1999 | This is a community-based RCT where they used WHO standard ORS of 311 osmol/L and reduced osmolarity ORS of 224 osmol/L. None of their outcomes were relevant for this review  |
| India 1978         | In this RCT, they used solution A (sodium 90 mmol/L, potassium 15 mmol/L, chlorine 75 mmol/L, bicarbonate 30 mmol/L, glucose 90 mmol/L) and B (sodium 50 mmol/L, potassium 15 mmol/L, chlorine 50 mmol/L, bicarbonate 15 mmol/L, glucose 170 mmol/L). Both solutions have total osmolarity of 300 mosmol/L |
| India 1984b        | In this randomized study, they compared WHO standard ORS (sodium 90 mmol/L, potassium 20 mmol/L, bicarbonate 30 mmol/L, chlorine 80 mmol/L, and glucose 111 mmol/L, total 331 mmol/L) and glycine fortified ORS of which osmolarity is not lower because 111 mmol/L of glycine was added                   |
| Iran 1983          | They compared sucrose high sodium (sodium 90 mmol/L, sucrose 111 mmol/L, total 331 osmol/L) and sucrose low sodium (sodium 58 mmol/L, total 278 osmol/L) ORS. They did not use WHO standard ORS  |
| Mexico 1988        | Appears to contain same patients as Mexico 1990a.  |
| Mexico 1990b       | Appears to contain same patients as Mexico 1990a.  |
| Myanmar 1991       | They compared WHO standard ORS (311 mmol/L) and maltodextrin/glycine/cycl-cycl-cycline ORS (326 mmol/L). They did not use reduced osmolarity ORS   |
| Russia 1997        | They compared WHO standard ORS (331 mmol/L), low ORS (224 mmol/L), and IV fluid infusion, and secondarily lactobacillus GG or placebo. None of their outcomes were relevant for this review  |
| Turkey 1985        | This is not an RCT but a comparison of data between two separate studies using ORS-60 and ORS-90   |
| Turkey 1986        | This is not an RCT but a comparison between treatment effects of ORS-60 (sodium 60 mmol/L) in malnourished infants with infectious diarrhoea and in a previous study of well-nourished patients. This paper is not an RCT but a comparison of data between two separate studies                            |
| USA 1972           | They used two hypotonic solutions. This is not an RCT. They did not use WHO standard ORS   |
| USA 1986           | They used solution A (sodium 50 mmol/L, glucose 111 mEq/L, 389 mosmol/L) and B (sodium 50 mmol/L, glucose 111 mEq/L, 278 mosmol/L). Solution A had 111 mEq/L of glycine additionally. They did not use WHO standard ORS  |

IV: intravenous; ORS: oral rehydration solution; RCT: randomized controlled trial; WHO: World Health Organization.

## DATA AND ANALYSES

### Comparison 1. Reduced osmolarity ORS compared to WHO standard ORS

| Outcome or subgroup title  | No. of studies | No. of participants | Statistical method                       | Effect size          |
|--|----------------|---------------------|--|----------------------|
| 1 Need for unscheduled intravenous fluid infusion                        | 11             | 1996                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.59 [0.45, 0.79]    |
| 2 Stool output   | 11             | 1776                | Std. Mean Difference (IV, Fixed, 95% CI) | -0.23 [-0.33, -0.14] |
| 3 Episode of vomiting during rehydration                                 | 6              | 1305                | Peto Odds Ratio (Peto, Fixed, 95% CI)    | 0.71 [0.55, 0.92]    |
| 4 Presence of hyponatremia after rehydration                             | 6              | 1120                | Peto Odds Ratio (Peto, Fixed, 95% CI)    | 1.44 [0.93, 2.24]    |
| 5 Need for unscheduled intravenous fluid infusion (sensitivity analysis) | 7              | 1688                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.61 [0.46, 0.82]    |
| 6 Stool output (sensitivity analysis)                                    | 6              | 1550                | Std. Mean Difference (IV, Fixed, 95% CI) | -0.21 [-0.31, -0.11] |

### Comparison 2. Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS

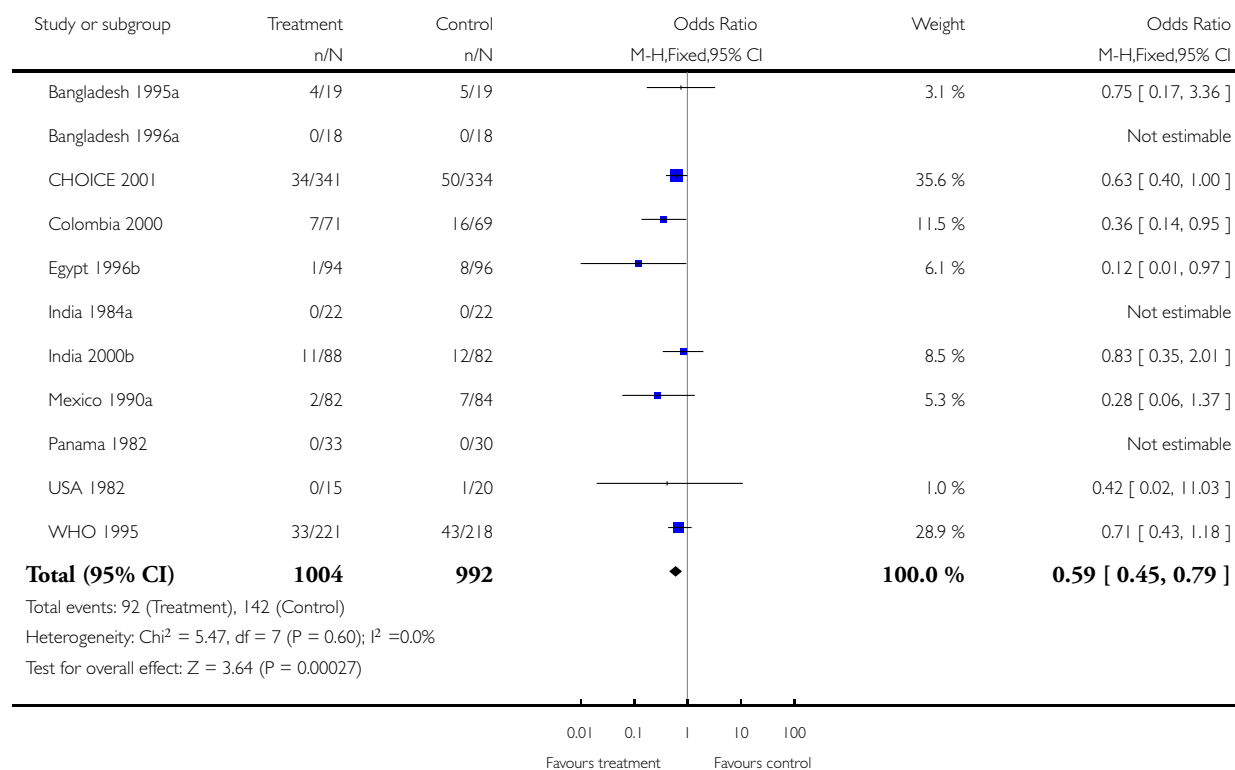
| Outcome or subgroup title                         | No. of studies | No. of participants | Statistical method                       | Effect size          |
|---|----------------|---------------------|--|----------------------|
| 1 Need for unscheduled intravenous fluid infusion | 9              | 1925                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.59 [0.44, 0.78]    |
| 1.1 60 to 74 mmol                                 | 4              | 584                 | Odds Ratio (M-H, Fixed, 95% CI)          | 0.70 [0.43, 1.15]    |
| 1.2 75 mmol to 84 mmol                            | 5              | 1341                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.53 [0.37, 0.76]    |
| 2 Stool output                                    | 7              | 1591                | Std. Mean Difference (IV, Fixed, 95% CI) | -0.20 [-0.30, -0.10] |
| 2.1 60 to 74 mmol                                 | 4              | 586                 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.31 [-0.47, -0.15] |
| 2.2 75 to 84 mmol                                 | 3              | 1005                | Std. Mean Difference (IV, Fixed, 95% CI) | -0.13 [-0.26, -0.01] |
| 3 Episodes of vomiting                            | 6              | 1305                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.70 [0.54, 0.91]    |
| 3.1 60 to 74 mmol                                 | 2              | 104                 | Odds Ratio (M-H, Fixed, 95% CI)          | 0.59 [0.24, 1.47]    |
| 3.2 75 to 84 mmol                                 | 4              | 1201                | Odds Ratio (M-H, Fixed, 95% CI)          | 0.71 [0.54, 0.93]    |
| 4 Presence of hyponatraemia                       | 6              | 1171                | Odds Ratio (M-H, Fixed, 95% CI)          | 1.45 [0.93, 2.26]    |
| 4.1 60 to 74 mmol                                 | 3              | 190                 | Odds Ratio (M-H, Fixed, 95% CI)          | 0.0 [0.0, 0.0]       |
| 4.2 75 to 84 mmol                                 | 3              | 981                 | Odds Ratio (M-H, Fixed, 95% CI)          | 1.45 [0.93, 2.26]    |

# **Analysis 1.1. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 1 Need for unscheduled intravenous fluid infusion.**

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 1 Need for unscheduled intravenous fluid infusion

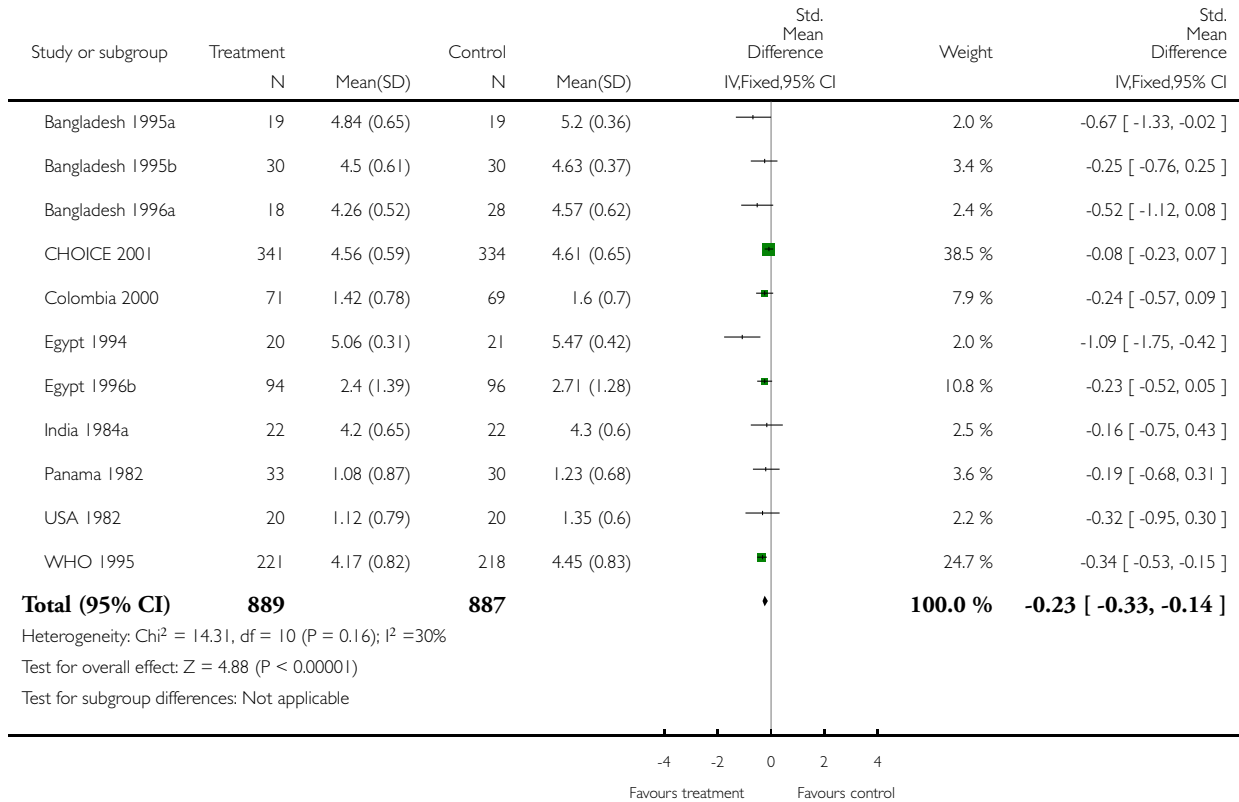


## Analysis 1.2. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 2 Stool output.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 2 Stool output



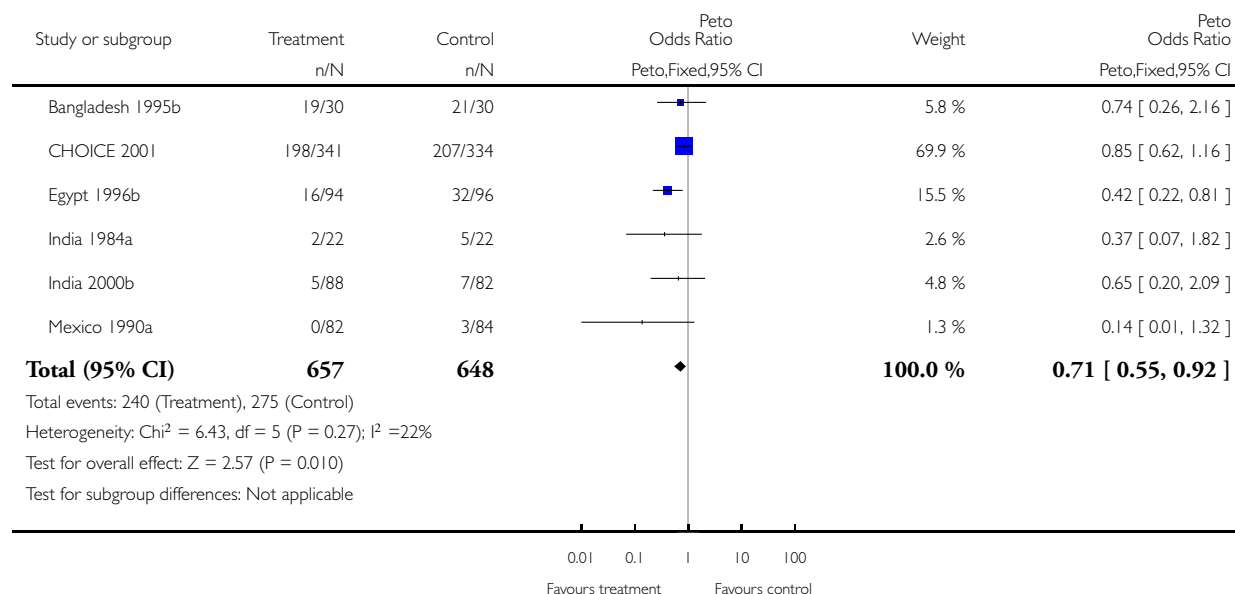


### Analysis 1.3. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 3 Episode of vomiting during rehydration.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 3 Episode of vomiting during rehydration

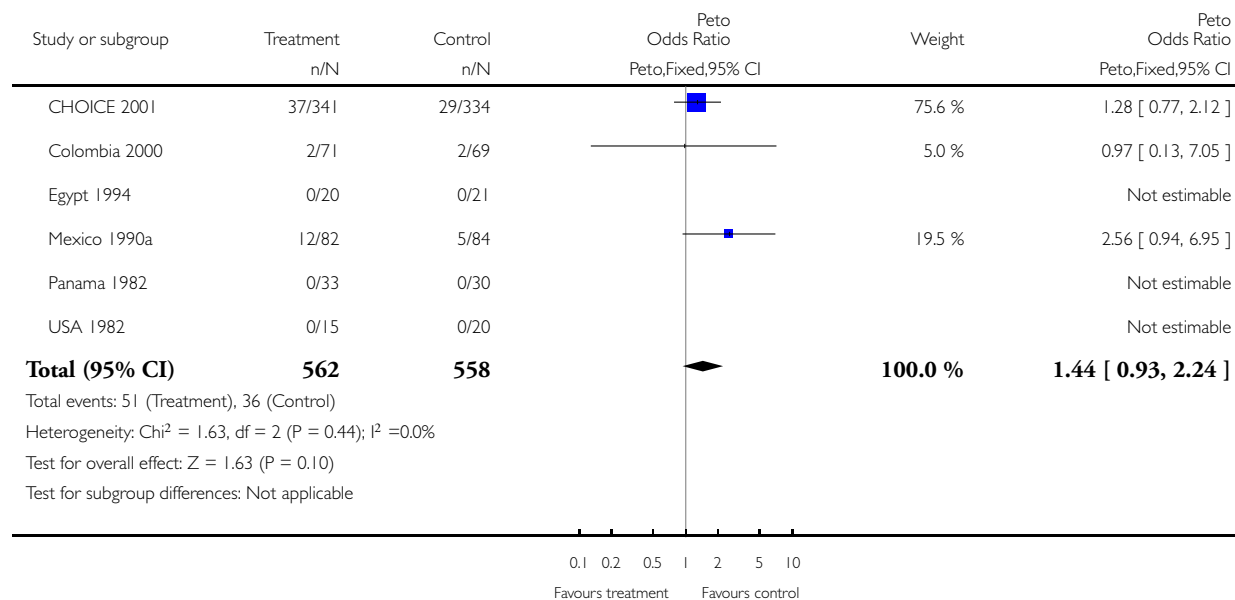


#### Analysis 1.4. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 4 Presence of hyponatremia after rehydration.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 4 Presence of hyponatremia after rehydration

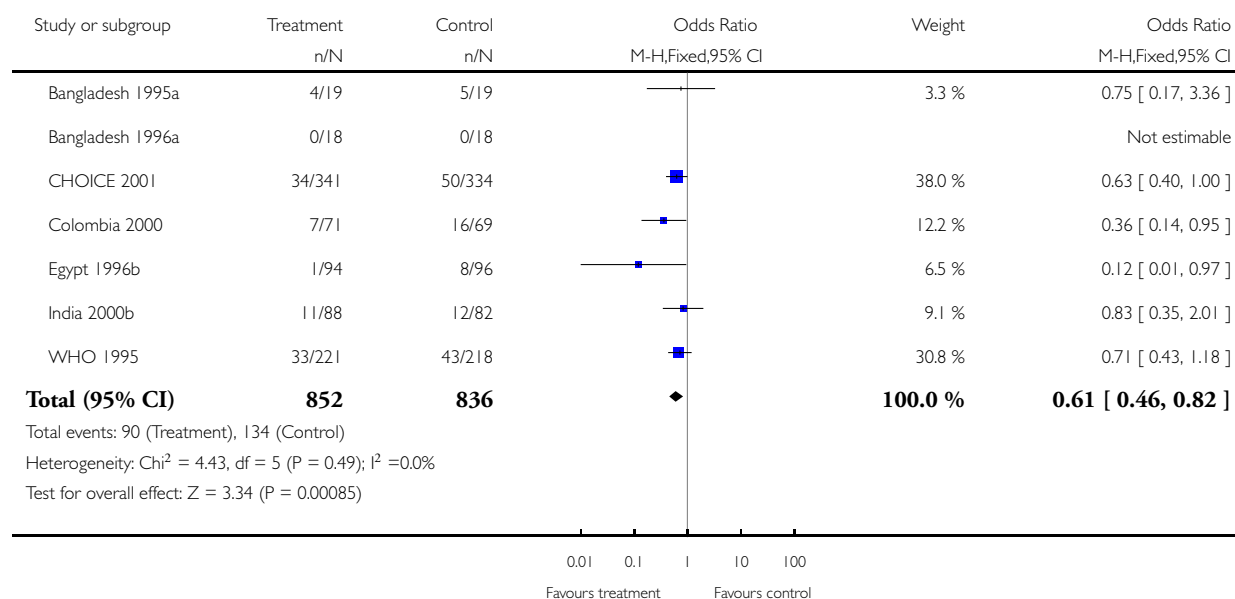


### Analysis 1.5. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 5 Need for unscheduled intravenous fluid infusion (sensitivity analysis).

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 5 Need for unscheduled intravenous fluid infusion (sensitivity analysis)

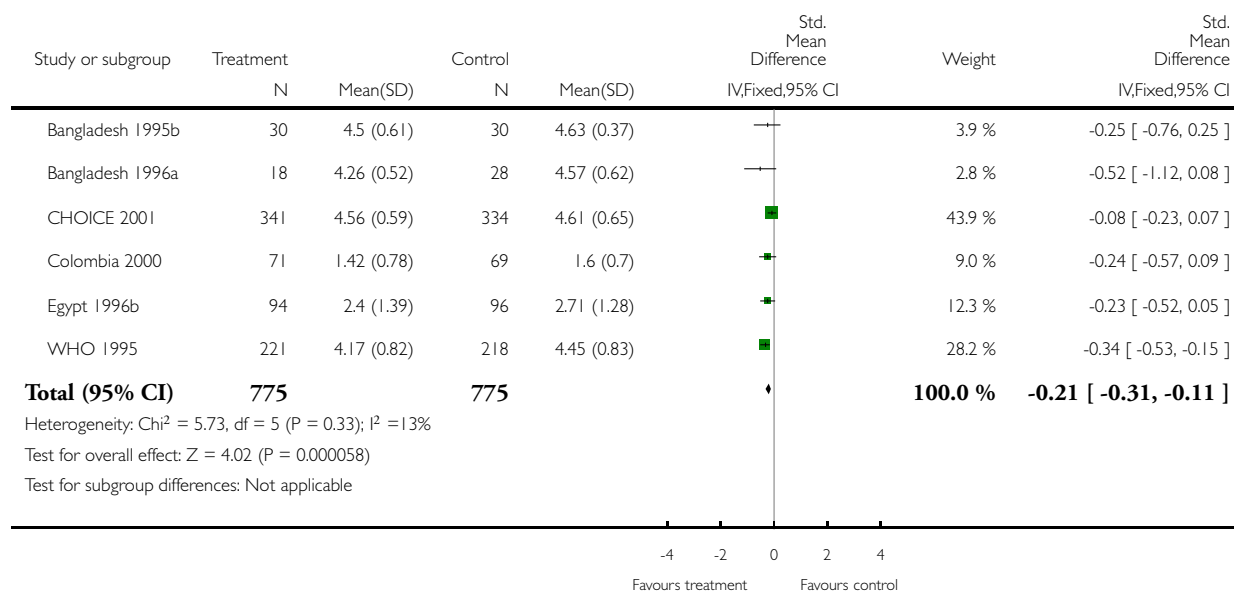


## Analysis 1.6. Comparison 1 Reduced osmolarity ORS compared to WHO standard ORS, Outcome 6 Stool output (sensitivity analysis).

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 1 Reduced osmolarity ORS compared to WHO standard ORS

Outcome: 6 Stool output (sensitivity analysis)

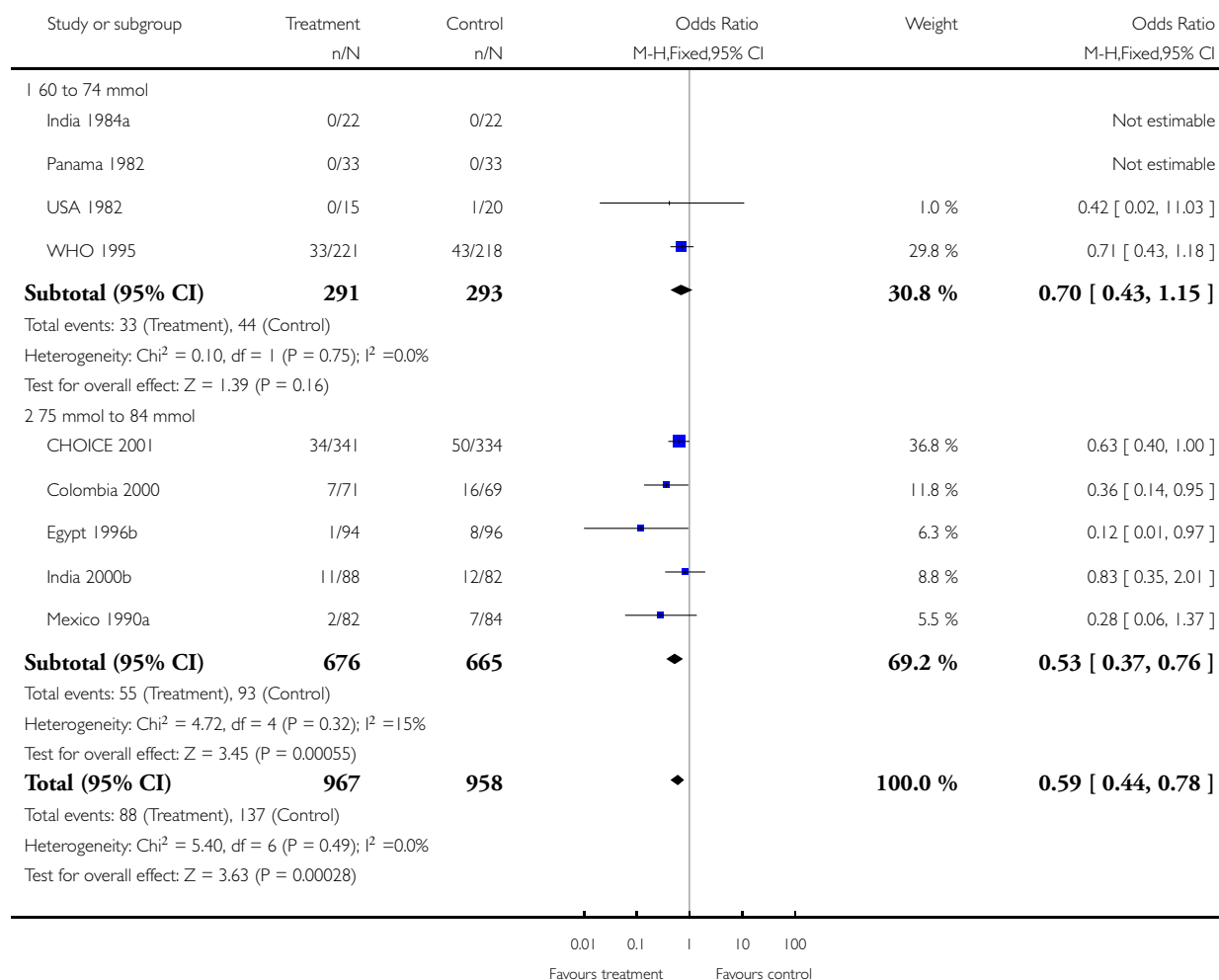


## Analysis 2.1. Comparison 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS, Outcome 1 Need for unscheduled intravenous fluid infusion.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS

Outcome: 1 Need for unscheduled intravenous fluid infusion

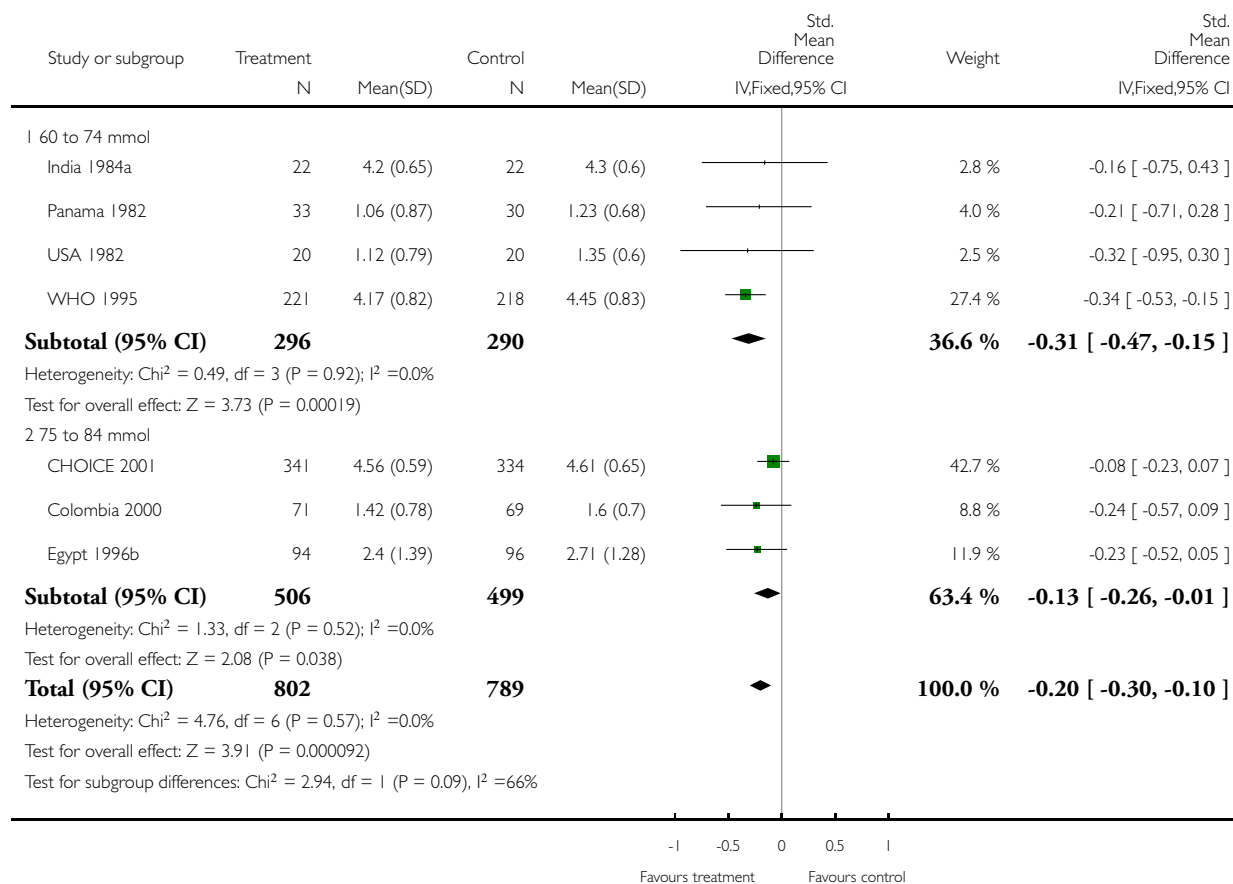


## Analysis 2.2. Comparison 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS, Outcome 2 Stool output.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS

Outcome: 2 Stool output

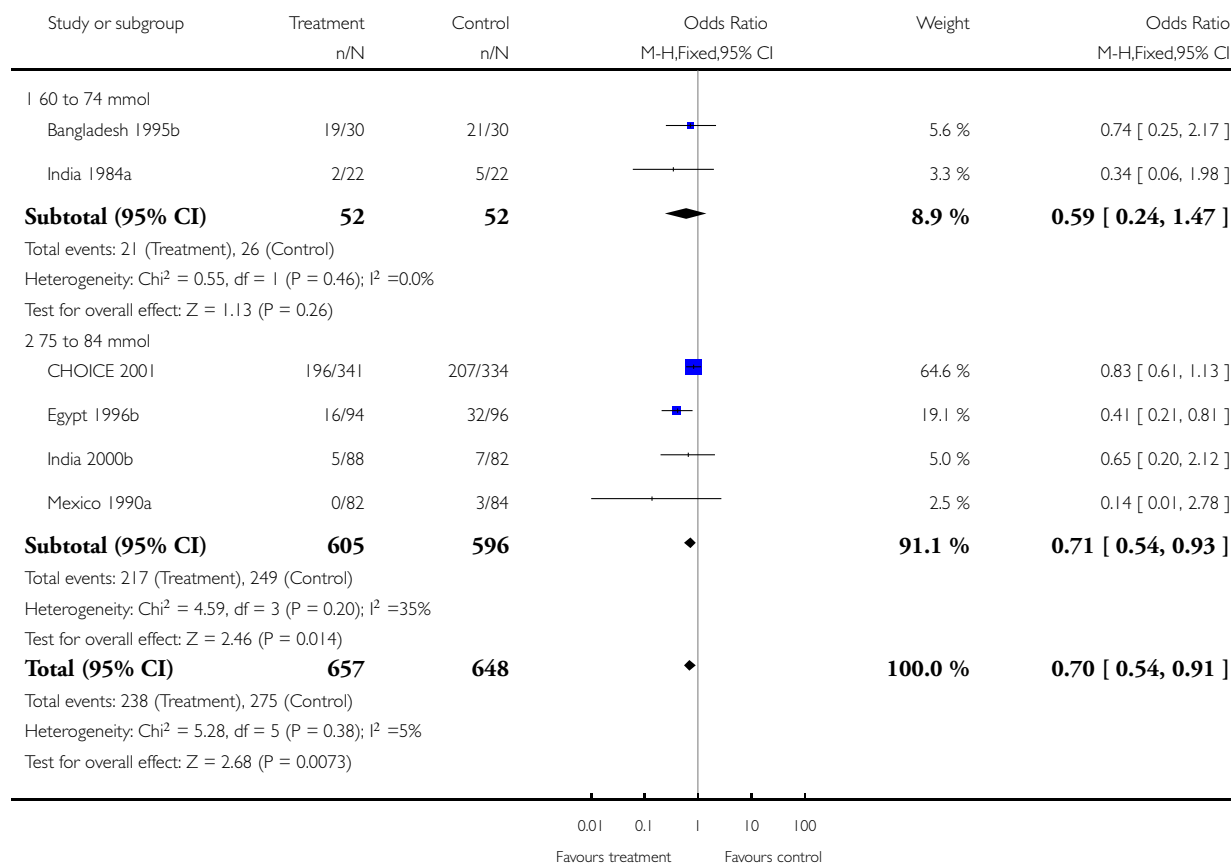


### Analysis 2.3. Comparison 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS, Outcome 3 Episodes of vomiting.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS

Outcome: 3 Episodes of vomiting



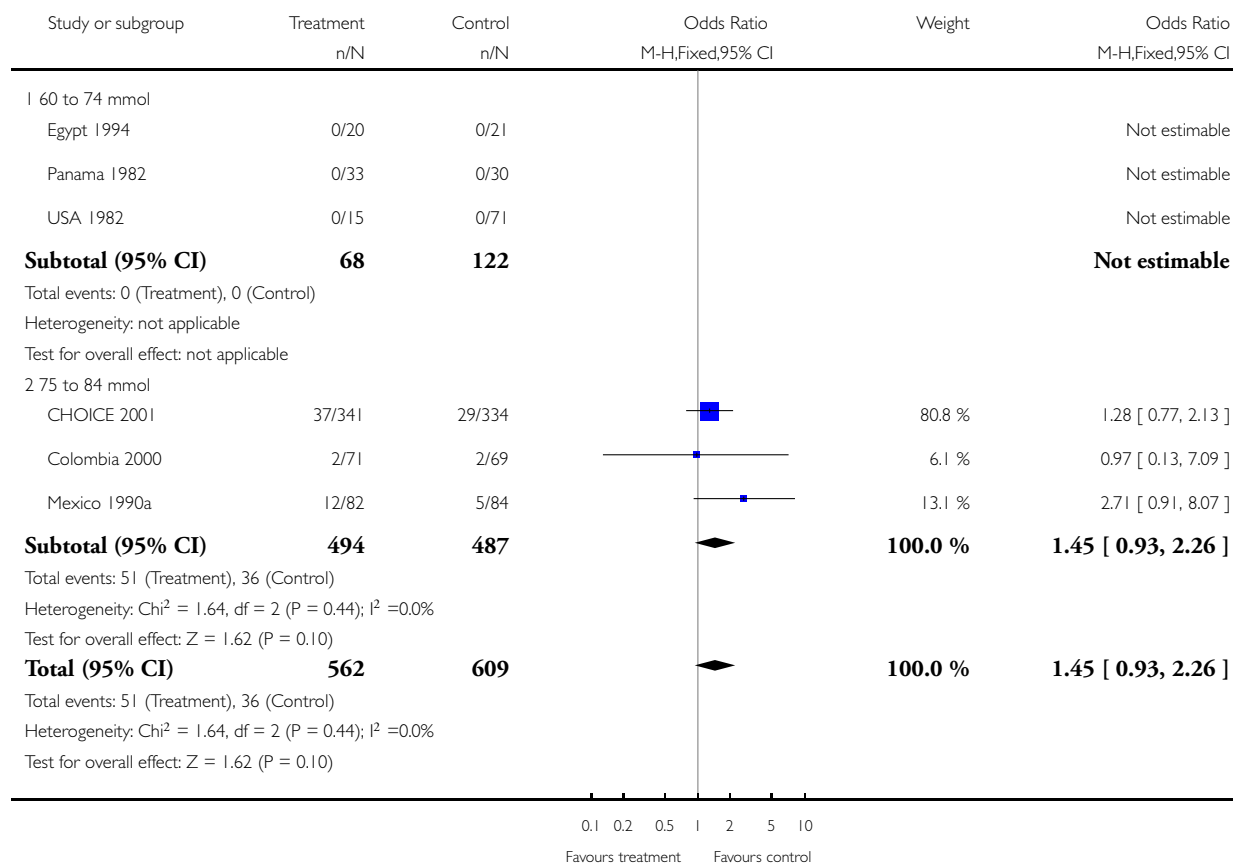


## Analysis 2.4. Comparison 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS, Outcome 4 Presence of hyponatraemia.

Review: Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison: 2 Reduced osmolarity ORS (stratified by sodium concentration) compared to WHO standard ORS

Outcome: 4 Presence of hyponatraemia



## APPENDICES

### Appendix I. Stool output

| Trials                   | Outcome   | Value           | ORS  |  | Differences   |
|--------------------------|---|-----------------|--|--|---|
|                          |   |                 | Low osmolarity                                       | WHO standard   |   |
| WHO 1995                 | Stool output at 24 h (g/kg)                     | Geometric mean  | n = 221; mean = 65; 95% confidence interval 58 to 73 | n = 218; mean = 86; 95% confidence interval 77 to 96 | Ratio standard/reduced = 1.32<br>95% confidence interval 1.12 to 1.54 |
| India 2000a              | Stool output during observation period (g/kg/d) | Arithmetic mean | n = 33; mean = 61.0; standard deviation = 24.5       | n = 37; mean = 75.0; standard deviation = 29.4       | -   |
| Egypt 1996b              | Stool output for re-hydration phase (g/kg)      | Geometric mean  | n = 94; mean = 11; 95% confidence interval 8 to 14   | n = 96; mean = 15; 95% confidence interval 12 to 20  | -   |
| Bangladesh 1995a         | Stool output at 0 to 24 h (ml/kg)               | Arithmetic mean | n = 19; mean = 156; standard deviation = 113.4       | n = 19; mean = 193; standard deviation = 71.2        | -   |
| Colombia 2000            | Stool output for re-hydration period (g/kg/h)   | Arithmetic mean | n = 71; mean = 5.6; standard deviation = 5.1         | n = 69; mean = 6.3; standard deviation = 5.0         | -   |
| Egypt 1994               | Stool output at 24 h (g/kg)                     | Arithmetic mean | n = 20; mean = 165; standard deviation = 52          | n = 21; mean = 260; standard deviation = 114         | -   |
| Bangladesh 1995b         | Stool output at 0 to 24 h (ml/kg)               | Arithmetic mean | n = 30; mean = 109; standard deviation = 73.8        | n = 30; mean = 110; standard deviation = 42.7        | -   |
| Bangladesh 1996a         | Stool output at 0 to 24 h (g/kg)                | Arithmetic mean | n = 18; mean = 80.9; standard deviation = 45.3       | n = 28; mean = 117.8; standard deviation = 81.0      | -   |
| India 1984a; India 1984b | Stool output at 24 h (ml/kg)                    | Arithmetic mean | n = 22; mean = 82.3; standard deviation = 60         | n = 22; mean = 88.1; standard deviation = 58.2       | -   |
| Panama 1982              | Stool output during first 8 h (ml/kg/h)         | Arithmetic mean | n = 33; mean = 4.3; standard deviation = 4.6         | n = 30; mean = 4.3; standard deviation = 3.3         | -   |

(Continued)

|             |   |                 |  |  |   |
|-------------|---|-----------------|--|--|---|
| USA 1982    | Stool output during the first 8 h (ml/kg/h) | Arithmetic mean | n = 15; mean = 4.2; standard deviation = 3.9   | n = 20; mean = 4.6; standard deviation = 4.0   | - |
| CHOICE 2001 | Stool output at 24 h (g/kg)                 | Arithmetic mean | n = 341; mean = 114; standard deviation = 73.9 | n = 334; mean = 125; standard deviation = 91.4 | - |

## WHAT'S NEW

| Date            | Event   | Description  |
|-----------------|---------|--|
| 22 October 2008 | Amended | Converted to new review format with minor editing. |

## HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 2, 2001

| Date             | Event   | Description  |
|------------------|---------|--|
| 27 July 2004     | Amended | New studies found but not yet included or excluded.  |
| 27 November 2001 | Amended | Changes made in response to feedback from specialists at the WHO/UNICEF oral rehydration salts formulation expert consultation. New York, 18 July 2001 <ol style="list-style-type: none"><li>1. Seizures outcomes to be sought (changes in progress)</li><li>2. <a href="#">Egypt 1996a</a> testing maltodextran excluded</li><li>3. Secondary analysis stratifying by sodium levels (60 to 74, 75 to 85 mmol)</li></ol> |

## CONTRIBUTIONS OF AUTHORS

Seokyoung Hahn and Yaejean Kim wrote the protocol, conducted the data extraction, data analysis and interpretation, and drafted the paper. Paul Garner advised on inclusion criteria and outcomes for the protocol, quality assessment and analysis, and helped write the review. Paul Garner is the guarantor.

## DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (eg employment, consultancy, stock ownership, honoraria, expert testimony).

The World Health Organization provided funds for us to conduct this review.

## SOURCES OF SUPPORT

### Internal sources

- Liverpool School of Tropical Medicine, UK.
- Medical and Pharmaceutical Statistics Research Unit, University of Reading, UK.
- Seoul National University Hospital, Korea, South.

### External sources

- World Health Organization, Switzerland.
- Department for International Development, UK.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Bicarbonates; Dehydration [etiology; \*therapy]; Diarrhea [\*complications]; Fluid Therapy [\*methods]; Glucose; Osmolar Concentration; Potassium Chloride; Rehydration Solutions [\*therapeutic use]; Sodium Chloride

### MeSH check words

Child, Preschool; Humans; Infant